Low dose ionizing radiation (IR) signaling regulation *in vivo* versus *in vitro* of the IGF-1/IGF-1R pathway leading to the synthesis of pro-survival secretory clusterin expression: Roles for p53/Hdm2. *Eva Cataldo, David Wilson, Lakshmi Sampath, Shinako Araki, Yonglong Zou, Bhavani Shankar, Lindsey Mayo, and David A. Boothman, Laboratory of molecular stress responses, University of Texas Southwestern Medical Center at Dallas, TX 75390.*

There are numerous circumstances under which humans can, and will, be exposed to low doses and dose rates of ionizing radiation; and this radiation can be very damaging (high linear energy transfer radiation) or less damaging (low energy transfer radiation). Unlike studies that examine responses of normal or tumor cells to clinically-relevant radiation exposures, low doses of radiation: (a) hit far fewer cells; (b) are not likely to yield the same kinds and extent of damage to the genetic material; and (c) are very poorly understood in terms of beneficial or harmful effects. Nevertheless, the question remains as to what level of radiation is harmful or possibly even beneficial (i.e., hormetic).

Previous studies from our lab indicated that human cells exposed to low doses of IR caused growth stimulation, speeding cells up in their cell cycle division (i.e., checkpoint regulation), as well as induced radiation resistance. A role for one x-ray-inducible protein-8 (xip8) was strongly indicated. Further studies showed that this gene was clusterin, a gene that ultimately makes a secreted protein (secretory clusterin, sCLU) that acts to clear cell debris, as well as prevent cell death responses (apoptosis). If sCLU synthesis was prevented, cells exposed to high challenging doses of IR were more effective. Thus, sCLU was cytoprotective. Further studies revealed that clusterin expression was regulated by the low dose damage-inducible production of the insulin-like growth factor-1 (IGF-1) cytokine. Downstream, the IGF-1R/Src/MAPK/Erk/Egr-1 pathway led to increased synthesis of this protein. Interestingly, p53 suppressed synthesis of the protein in cell culture.

We then generated a transgenic mouse containing the CLU promoter directing luciferase synthesis. Real time bioluminescence imaging (BLI) of these mice after IR revealed induction in the colon, spleen, thymus, and bone marrow after IR. Since these mice express wild-type p53, we investigated the mechanism of induction after low dose IR exposure. We discovered that IR activated TGF-ß1, which resulted in sCLU activation by simultaneous: (a) induction of Hdm2, formation of P-Hdm2 by AKT, and degradation of p53; and (b) stimulation of IGF-1 synthesis, which in turn activates the IGF-1R/Src/MAPK pathway leading to Smad- and AP-1-mediated induction of CLU expression. We will discuss the implications of this pathway in terms of DNA repair and survival. ***This work was funded by DOE grant DE-FG02-06ER64186 to DAB.***